# Prostate MRI: Evaluating tumor volume and apparent diffusion coefficient as surrogate biomarkers for predicting tumor Gleason score

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Abstract: Purpose To investigate whether tumor volume derived from apparent diffusion coefficient (ADC) maps (VolumeADC) and tumor mean ADC value (ADCmean) are independent predictors of prostate tumor Gleason score (GS). Materials and Methods Tumor volume and GS were recorded from whole-mount histopathology for 131 men (median age, 60) who underwent endorectal diffusion-weighted magnetic resonance imaging for local staging of prostate cancer before prostatectomy. VolumeADC and ADCmean were derived from ADC maps and correlated with histopathologic tumor volume and GS. Uni- and multivariate analyses were performed to evaluate prediction of tumor aggressiveness. Areas under receiver-operating-characteristics curves (AUCs) were calculated to evaluate the performance of VolumeADC and ADCmean in discriminating tumors of GS 6 and GS  7. Results Histopathology identified 116 tumor foci >0.5 mL. VolumeADC correlated significantly with histopathologic tumor volume ( =0.683). The correlation increased with increasing GS ( =0.453 for GS 6 tumors;  =0.643 for GS 7 tumors;  =0.980 for GS 8 tumors). Both VolumeADC ( =0.286) and ADCmean ( =-0.309) correlated with GS. At univariate analysis, both VolumeADC (p=0.0325) and ADCmean (p=0.0033) could differentiate GS=6 from GS 7 tumor foci. However, at multivariate analysis, only ADCmean (p=0.0156) was a significant predictor of tumor aggressiveness (i.e., GS 6 vs. GS  7). For differentiating GS 6 from GS 7 tumors, AUCs were 0.644 and 0.704 for VolumeADC and ADCmean, respectively, and 0.749 for both parameters combined. Conclusion In patients with prostate cancer, ADCmean is an independent predictor of tumor aggressiveness, but VolumeADC is not. The latter parameter adds little to the ADCmean in predicting tumor Gleason score.

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# Prostate MRI: Evaluating tumor volume and apparent diffusion coefficient as surrogate biomarkers for predicting tumor Gleason score

Running Title: Diffusion-weighted MRI in prostate cancer: prediction of aggressiveness

**Original Research**

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**Key Words**: Magnetic resonance imaging, diffusion-weighted, prostate cancer, biomarker, aggressiveness

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## Statement of Translational relevance:

Many prostate cancers diagnosed today are likely indolent, but better means of assessing prostate cancer prognosis are needed to identify the appropriate, patient-specific treatment option. Distinguishing tumors of Gleason score 6 from tumors of Gleason score ≥7 is especially critical for assessing eligibility for active surveillance (AS). In patients who underwent diffusion-weighed MRI before radical prostatectomy, we assessed the value of the mean tumor apparent diffusion coefficient ($ADC_{mean}$) and the tumor volume measured from ADC maps ($Volume_{ADC}$) for predicting two important prognostic factors: tumor volume and tumor Gleason score on histopathology. $Volume_{ADC}$ correlated well with histopathologic tumor volume, and the strength of the correlation increased with the tumor Gleason score. Both $Volume_{ADC}$ and $ADC_{mean}$ correlated with tumor Gleason score, but on multivariate analysis only $ADC_{mean}$ independently distinguished tumors of Gleason Score 6 from tumors of Gleason Score ≥7. Our findings indicate that independent of the tumor volume, $ADC_{mean}$ could serve as a biomarker to predict prostate cancer aggressiveness.

## Abstract

### Purpose

To investigate whether tumor volume derived from apparent diffusion coefficient (ADC) maps ($Volume_{ADC}$) and tumor mean ADC value ($ADC_{mean}$) are independent predictors of prostate tumor Gleason score (GS).

### Materials and Methods

Tumor volume and GS were recorded from whole-mount histopathology for 131 men (median age, 60) who underwent endorectal diffusion-weighted magnetic resonance imaging for local staging of prostate cancer before prostatectomy. $Volume_{ADC}$ and $ADC_{mean}$ were derived from ADC maps and correlated with histopathologic tumor volume and GS. Uni- and multivariate analyses were performed to evaluate prediction of tumor aggressiveness. Areas under receiver-operating-characteristics curves (AUCs) were calculated to evaluate the performance of $Volume_{ADC}$ and $ADC_{mean}$ in discriminating tumors of GS 6 and GS ≥7.

### Results

Histopathology identified 116 tumor foci >0.5 mL. $Volume_{ADC}$ correlated significantly with histopathologic tumor volume ($\rho$=0.683). The correlation increased with increasing GS ($\rho$=0.453 for GS 6 tumors; $\rho$=0.643 for GS 7 tumors; $\rho$=0.980 for GS≥8 tumors). Both $Volume_{ADC}$ ($\rho$=0.286) and $ADC_{mean}$ ($\rho$=-0.309) correlated with GS. At univariate analysis, both $Volume_{ADC}$ (p=0.0325) and $ADC_{mean}$ (p=0.0033) could differentiate GS=6 from GS≥7 tumor foci. However, at multivariate analysis, only $ADC_{mean}$ (p=0.0156) was

a significant predictor of tumor aggressiveness (i.e., GS 6 vs. GS ≥7). For differentiating GS 6 from GS≤7 tumors, AUCs were 0.644 and 0.704 for VolumeADC and $ADC_{mean}$, respectively, and 0.749 for both parameters combined.

**Conclusion**

In patients with prostate cancer, $ADC_{mean}$ is an independent predictor of tumor aggressiveness, but $Volume_{ADC}$ is not. The latter parameter adds little to the $ADC_{mean}$ in predicting tumor Gleason score.

## Introduction

It was estimated that 30% to 50% of the approximately 238,590 American men diagnosed with prostate cancer (PCa) in 2013 would have an indolent form of the disease unlikely to become life-threatening. These men could potentially take advantage of an increasing spectrum of patient-tailored disease management options—including active surveillance and various forms of focal ablation—that are designed to minimize adverse treatment-related effects (1-3). However, to ensure that patients are indeed suited for such conservative management approaches, it is essential not only to detect and localize PCa, but also to assess its aggressive potential—a task that remains challenging. Clinical, biochemical and pathological features are typically used to triage patients according to the likelihood of rapid disease progression (4-8).

Recently, diffusion-weighted magnetic resonance imaging (DWI) has garnered interest for its potential to non-invasively characterize PCa aggressiveness. DWI probes variations in free water movement within tissues, which tends to be more restricted in the presence of tumor due to changes in cell number, size and architecture. On DWI images, variations in water diffusion manifest as changes in signal intensity, and degrees of diffusion restriction can be assessed quantitatively by means of the apparent diffusion coefficient (ADC). A relatively simple metric, the ADC can be calculated on a pixel-by-pixel basis with clinical MRI platforms. A number of studies have shown an inverse correlation between ADC values on DWI and prostate cancer Gleason scores (9-14). However, the ADC values of PCa foci with different Gleason scores overlap, and no method has been developed to determine the Gleason score unequivocally based on ADC analysis alone (9-14).

Pathology studies have shown that higher tumor volumes are associated with higher Gleason scores and worse outcomes (15, 16). Tumor volume measured on DWI correlates well with the histopathologic tumor volume (17, 18). However, the relationship between ADC and prostate tumor volume and the potential synergy of these two parameters in evaluating PCa aggressiveness have not been explicitly explored. Thus, the purpose of our study was to investigate whether tumor mean ADC value and tumor volume derived from ADC maps are independent predictors of tumor Gleason score and can be used to distinguish tumors with Gleason scores of 6 from those with Gleason scores of 7 or above.

## Materials and Methods

The institutional review board approved our retrospective study and waived the informed consent requirement. Our study was compliant with the Health Insurance Portability and Accountability Act.

### Patients

Patients who underwent MRI of the prostate including DWI between July 2008 and April 2010 and for whom whole-mount step-section pathologic tumor maps were available were identified (n=377). Patients who met the following inclusion criteria were selected: 1) 1.5-Tesla MRI of the prostate, including a DWI sequence with b=0, 1000 s/mm$^2$; 2) radical prostatectomy performed at our institution within 6 months after MRI. Patients were excluded if a) they had undergone prior prostate cancer treatment, including hormone therapy or radiation; b) acquisition was incomplete or imaging artifacts rendering the examination non-diagnostic were present; or c) MRI was performed without an endorectal coil. Our final study population consisted of 131 consecutive patients who were previously included in a study analyzing histogram-derived apparent diffusion coefficient (ADC) parameters (19). Patients' characteristics are summarized in **Supplemental Table 1**.

### MRI Acquisition

All images were acquired on a 1.5-Tesla MRI system (GE Healthcare Technologies, Waukesha, WI). A body coil was used for excitation; a pelvic four-channel phased-array coil and an endorectal coil (Medrad, Warrendale, Pa) were used for signal reception. T1-weighted, T2-weighted and DWI sequences were acquired but only DWI sequence was used for analysis in this study. DWI was performed using a single-shot spin-echo echo-planar imaging sequence with b=0, 1000 s/mm$^2$ (TR/TE, 1200-6800ms/40-113ms; section thickness, 3-4mm; no intersection gap; FOV, 12-16 cm; matrix, 96 x 96 - 128 x 128). Parametric maps of ADC values were calculated using a designated workstation (Advanced Workstation, GE Medical Systems).

## MRI - Histopathologic Correlation

### *Histopathologic Preparation*

After prostatectomy, specimens were submitted to histopathology, where they were sliced from apex to base at 3-4-mm intervals. Microslices were placed on glass slides and stained with hematoxylin-eosin after paraffin embedding. For each patient, one of two dedicated genitourinary pathologists at our institution with more than 30 years of combined experience verified,and assigned a Gleason score for (GS) for each tumor outlined on the histology slides.

### *Measurement of Histopathologic Tumor Volume*

Tumor volume on pathology slices was measured in consensus by two of the authors using software (ImageJ, version 1.47a; National Institutes of Health, Bethesda, Md). If a lesion extended into more than one pathologic slice, the areas of tumor foci on all slices were summed to obtain an estimate of the histopathologic volume of the whole

lesion. Tumors that covered both zones - the transition zone (TZ) as well as the peripheral zone (PZ) - were considered to be TZ tumors if more than 70% of the tumor was in the TZ (20); all others were considered to be PZ tumors (9).

***Correlation of Lesions on MRI and Histopathology***

Working in consensus, three radiologists (with 1, 1 and 9 years of experience in interpreting prostate MRI,) correlated MR images with whole-mount pathology maps to establish the locations of tumors on MRI. Using software (ImageJ, version 1.47a; National Institutes of Health, Bethesda, Md), the radiologists drew a freehand region of interest around the discernible tumor tissue on the ADC maps (19). If a tumor was depicted on more than one slice, all traced ROIs corresponding to that tumor were included in the estimation of the tumor volume ($Volume_{ADC}$) and the calculation of the mean ADC value ($ADC_{mean}$) (19). On each slice containing tumor, the area of the tumor focus was determined on a voxel-basis by considering the acquisition matrix, reconstruction matrix as well as the FOV. $Volume_{ADC}$ [mL] was calculated as (sum of all tumor areas on the slices ($cm^2$) x slice thickness (cm)).

**Statistical Analysis**

The correlation between $Volume_{ADC}$ and volume derived from histopathology as well as the correlations of $Volume_{ADC}$ and $ADC_{mean}$ with tumor GS were assessed using Spearman's correlation coefficient ($\rho$). The between-subject correlation coefficient proposed by Bland and Altman (21) was calculated and tested to take into account multiple lesions per patient.

To evaluate whether $Volume_{ADC}$ and $ADC_{mean}$ could differentiate a GS of 6 from a GS ≥ 7, a generalized linear regression and generalized estimating equations method was used with an independent correlation structure and robust covariance matrix, to take into account multiple lesions per patient. Univariate and multivariate analyses with both $Volume_{ADC}$ and $ADC_{mean}$ as covariates were performed. The odds ratio (OR) describing the likelihood of a tumor having GS≥7, along with the 95% confidence interval (CI), was estimated. Nonparametric receiver operating characteristic (ROC) curve analysis was performed, and the area under the curve (AUC) was estimated to evaluate the performance of $Volume_{ADC}$ and $ADC_{mean}$ in discriminating between GS 6 and GS≥7. Sensitivity and specificity based on the estimated probabilities from the multivariate model were used to estimate the AUC for the combination of both variables.

All statistical analyses were performed with SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and R version 2.13 (The R Foundation for Statistical Computing). Results with p-values $< 0.05$ were considered statistically significant.

## Results

Forty-six patients presenting only insignificant cancer lesions in terms of volume (≤0.5mL) (22) were excluded from comparative analysis. One hundred sixteen clinically significant lesions (>0.5mL) on histopathology were found in 85 patients. Eighty-nine (76.7%) of the 116 lesions originated in the PZ and 27/116 (23.3%) originated in the TZ. Lesion characteristics including tumor volume and GS are shown in **Supplemental Table 2**.

### Correlation of $Volume_{ADC}$ and Histopathologic Tumor Volume

The Spearman's correlation coefficient for $Volume_{ADC}$ and histopathologic tumor volume in lesions >0.5 mL was $\rho$=0.683 (p<0.0001) (**Figure 1**). The correlation coefficient increased as the tumor GS increased, rising from $\rho$=0.453 (p=0.1042) for tumors with a GS of 6 (3+3), to $\rho$=0.643 (p<0.0001) for tumors with a GS of 7 (3+4 or 4+3) and $\rho$=0.980 (p<0.0001) for tumors with a GS ≥ 8 (**Table 1**). The correlation between histopathologic tumor volume and $Volume_{ADC}$ was highest for tumors of GS≥8.

### Correlations of Histopathologic Tumor Volume, $Volume_{ADC}$ and $ADC_{mean}$ with GS

Histopathologic tumor volume and $Volume_{ADC}$ both correlated positively with tumor GS ($\rho$=0.336 [p=0.0017] and $\rho$=0.286 [p=0.0081], respectively), while $ADC_{mean}$ correlated negatively with tumor GS ($\rho$=-0.309 [p=0.0087]).

**Differentiation of Tumor Aggressiveness by $Volume_{ADC}$ and $ADC_{mean}$**

In a univariate analysis including all lesions (PZ and TZ), both $Volume_{ADC}$ and $ADC_{mean}$ could differentiate tumors of GS 6 from those with a GS ≥ 7 (odds ratio, 1.73 for $Volume_{ADC}$ and 0.64 for $ADC_{mean}$; p-values, p=0.0325 and p=0.0033, respectively) (**Table 2**). In a sub-analysis considering only tumors originating in the PZ, $ADC_{mean}$,could differentiate between tumors of GS 6 and those with a GS ≥ 7 (p=0.0025), but $Volume_{ADC}$ could not (p=0.2709) (**Table 2**). The number of lesions originating in the TZ was too small to permit a sub-analysis.

In a multivariate analysis, after adjustments were made for the influence of $Volume_{ADC}$, $ADC_{mean}$ independently discriminated between tumors of GS 6 and tumors with a GS ≥ 7 (p=0.0156) (**Figure 2**). However, after adjustments were made for the influence of $ADC_{mean,}$ $Volume_{ADC}$ could not independently differentiate between these two tumor Gleason score categories (p=0.0733) (**Table 2, Figure 3**).

Accuracy in discriminating tumors of GS 6 from those with a GS ≥ 7 was slightly lower for $Volume_{ADC}$ than for $ADC_{mean}$ (AUC=0.644 and AUC=0.704, respectively; p=0.3262). Combining these variables as covariates in a multivariate model resulted in a minor increase in AUC (to 0.749) (**Supplemental Figure 1**).

## Discussion

In our study, tumor volume measured on ADC maps correlated with tumor volume on histopathology, and the strength of the correlation increased with the tumor Gleason score. In addition, the tumor mean ADC value - but not the tumor volume derived from ADC maps - independently differentiated tumors of Gleason score 6 from those of Gleason score 7 or above. The tumor volume derived from ADC maps ($Volume_{ADC}$) added little to the tumor mean ADC value ($ADC_{mean}$) in predicting the tumor Gleason score.

The correlation between $Volume_{ADC}$ and histopathologic tumor volume in our study (Spearman's correlation coefficient [$\rho$] = 0.68) was very similar to that reported by Isebaert et al. ($\rho$=0.75) (17), and it was slightly higher than the correlation between tumor volume on T2-weighted MRI and histopathologic tumor volume reported by Turkbey et al. ($\rho$=0.63) (23). The difference between our result and that of Turkbey et al. is consistent with an earlier study by Mazaheri et al., which found that prostate cancer tumor volume measurements based on ADC maps correlated better with histopathologic tumor volumes than did measurements based on T2-weighted MRI (17, 18). Furthermore, the correlation between imaging- and histopathology-derived tumor volumes may have been stronger in our study because, unlike Turkbey et al., we used a pixel-based calculation to determine imaging and histopathologic tumor volumes, outlining tumor borders instead of using the ellipsoid formula, which is based on linear measurements and does not take into account the irregular shapes of PCa foci.

In keeping with the existing literature, we demonstrated that ADC-based tumor volume and histopathologic tumor volume correlate better in PCa foci with higher Gleason scores. This may be explained by the fact that tumors with higher Gleason scores are better depicted on ADC maps because they contrast more strongly with benign tissue (10, 13); this makes it easier to trace the borders of the lesions and likely results in more accurate representations of the actual areas of tumor on ADC maps.

The correlation between $Volume_{ADC}$ and GS in our study ($\rho$=0.29) was similar to that recently reported by Verma et al. ($\rho$=0.35) (24). Likewise the correlation between $ADC_{mean}$ and GS in our patient cohort ($\rho$=-0.31) was within the range of such correlations reported in recent studies ($\rho$=-0.26 to -0.38) (12, 14, 24). At multivariate analysis, $ADC_{mean}$ was the only parameter that independently predicted the category of the tumor GS (GS 6 vs. GS ≥ 7). It appears that though the predictive value of $ADC_{mean}$ for tumor aggressiveness is independent of tumor size, when $ADC_{mean}$ is not clearly predictive, $Volume_{ADC}$ cannot be used to resolve the ambiguity. These results contrast with those of a recent study by Verma et al., in which both mean ADC value and $Volume_{ADC}$ were identified as significant predictors of tumor aggressiveness in the PZ at multivariate analysis (24). There are several possible reasons for the discrepancy. First, different statistical methods were used for the multivariate analyses of the two studies. Second, our measurements were based on whole-mount step-section pathology slides instead of recreated histologic maps. Third, the b-values used to create the ADC maps in our patient cohort (b=0, 1000 s/mm$^2$) differed from those used in the other study (b=0, 600 s/mm$^2$) (24). (ADC values are dependent on the chosen b-values (25), and therefore ADC measurements cannot be compared between protocols using

different b-values. However, as long as the imaging parameters, including the b-value, are kept constant, ADC values measured in the abdomen may be comparable across different scanners and field strengths (26)). Fourth, in the study by Verma et al., only the voxels of the most central slice were used to calculate ADC parameters. Although the results of the multivariate analyses differed, accuracy levels in identifying PCa foci of GS ≥ 7 by combining $ADC_{mean}$ and $Volume_{ADC}$ were similar in the two studies (24).

We acknowledge the following limitations of our study: First, so that we would be able to correlate imaging findings with histopathology, we only included patients who underwent radical prostatectomy, causing a selection bias. Therefore our results may not apply to a broader population of patients with newly diagnosed prostate cancer, especially since there is a trend for increasing use of active surveillance of low-risk prostate cancer (27). However, this selection bias is inherent to every study that uses whole-mount step-section histopathology specimens as a reference standard for evaluating imaging variables. Second, an endorectal coil was used for acquisition of MRI, potentially deforming the prostate gland and the tumor foci. However, the use of an endorectal coil provides a higher signal-to-noise ratio (28) and may therefore be preferable for quantitative ADC analysis. Third, our approach of retrospectively delineating the prostate cancer foci on ADC maps using the histopathology maps as a guide does not represent the sequence of events in the clinical setting, where histopathology maps would not be available at the time of MRI. Therefore, we are not able to provide information on the accuracy of prostate cancer detection in this study or on the effect that potentially missed lesions might have had on our results. Furthermore, using histopathology slices for identification of tumor foci may have introduced a

potential bias in the evaluation of lesion volume on ADC maps as the location of tumors was available to the radiologists encircling the tumor foci. Although, the ROI drawn by the radiologists for the purposes of this study only contained clearly discernible tumor tissue on ADC maps (e.g. voxels that were visually darker than the surrounding healthy tissue), we acknowledge that the correlations reported in this study would be influenced by the diagnostic accuracy of prostate cancer detection in routine clinical practice.

In summary, our results suggest that while $Volume_{ADC}$ is useful to predict true tumor volume, $ADC_{mean}$ is the more useful parameter for distinguishing between GS 6 and higher-Gleason-score tumors – a distinction that is critical for identifying suitable candidates for active surveillance.

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Dr. Afaq was a European School of Radiology Visiting Scholar and is currently a researcher at the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

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# Tables

## Table 1 – Correlation between Tumor Volume on Histopathology and Tumor Volume on ADC Maps

| | ρ | p-value | Lesions | Patients |
|---|---|---|---|---|
| **All tumors** | 0.683 | <.0001 | 116 | 85 |
| **PZ Tumors** | 0.706 | <.0001 | 89 | 73 |
| **TZ Tumors** | 0.677 | 0.0003 | 27 | 24 |
| **GS 6 Tumors** | 0.453 | 0.1042 | 16 | 14 |
| **GS 7 Tumors** | 0.643 | <.0001 | 92 | 71 |
| **GS ≥8 Tumors** | 0.980 | <.0001 | 8 | 8 |

Note: ρ = Spearman's correlation coefficient; PZ=peripheral zone; TZ=transition zone; GS = Gleason score. 95%CI was estimated using the bootstrapping method of resampling patients.

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Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

**Table 2 – Results of Univariate and Multivariate Analyses for Prediction of Tumor Gleason score ≥7 by Mean Tumor ADC ($ADC_{mean}$) and Tumor Volume Derived from ADC Maps ($Volume_{ADC}$)**

| | All lesions >0.5 mL | | PZ lesions >0.5 mL | |
|---|---|---|---|---|
| | OR (95%CI) | p-Value | OR (95%CI) | p-Value |
| | **Univariate Analysis** | | | |
| **$ADC_{mean}$** (100-unit increment) | 0.64 (0.47, 0.86) | 0.0033 | 0.50 (0.32, 0.78) | 0.0025 |
| **$Volume_{ADC}$** (0.5 mL increment) | 1.73 (1.05, 2.87) | 0.0325 | 1.50 (0.73, 3.07) | 0.2709 |
| | **Multivariate Analysis** | | | |
| **$ADC_{mean}$** (100-unit increment) | 0.68 (0.50, 0.93) | 0.0156 | 0.51 (0.33, 0.79) | 0.0025 |
| **$Volume_{ADC}$** (0.5 mL increment) | 1.57 (0.96, 2.59) | 0.0733 | 1.14 (0.66, 1.98) | 0.6359 |

Note: PZ= peripheral zone.

**Odds ratio (OR) interpretation**: the tumors are less likely to have a Gleason score of 7 or above as the $ADC_{mean}$ increases (OR for 100-unit increase = 0.68, 95%CI: 0.50-0.93), controlling for $Volume_{ADC}$.

Transition zone tumors were not assessed separately due to the small number of lesions in the transition zone.

## Figure Captions

**Figure 1 –** Correlation of tumor volume derived from histopathology and tumor volume derived from ADC maps.

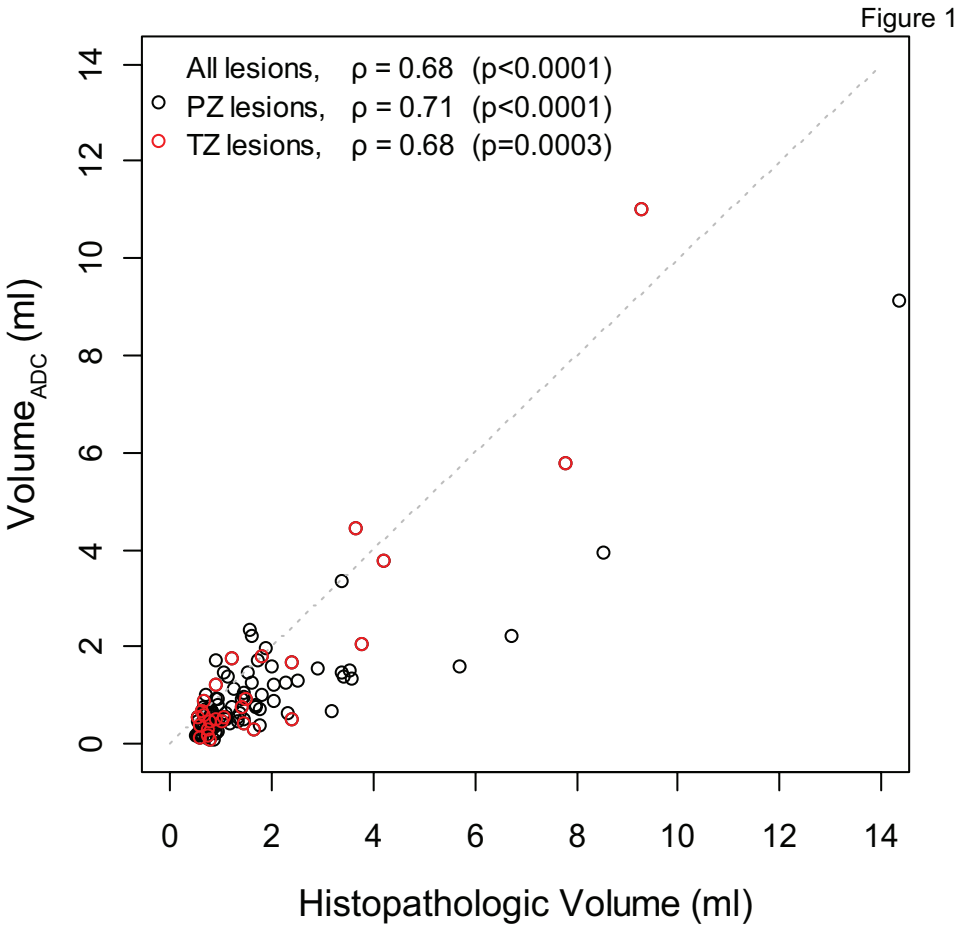
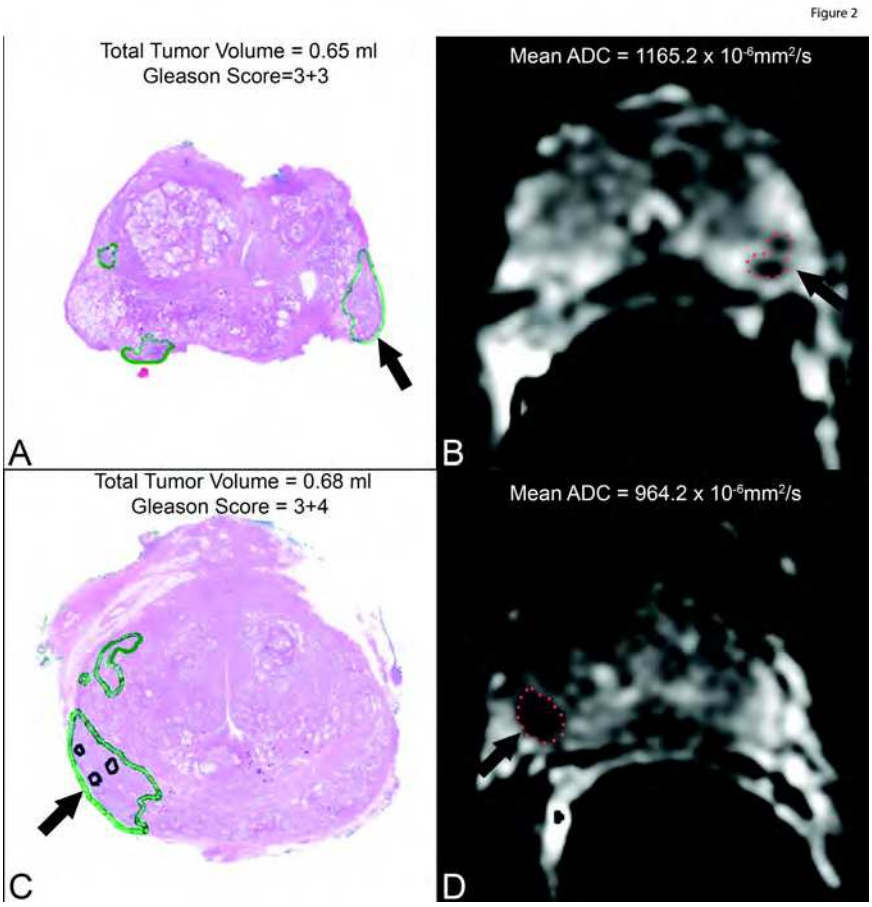


**Figure 2** – Top row: Whole-mount histopathology slice (A) and ADC map (b=0, 1000 s/mm$^2$) (B) demonstrating a PCa focus with a Gleason score of 3+3 (arrows), a total tumor volume of 0.65 mL and a mean ADC of 1165.2 *10-6 mm$^2$/s. The bottom row shows the whole-mount histopathology slice (C) and ADC map (b=0, 1000 s/mm$^2$) (D) of a PCa focus with a Gleason score of 3+4 (arrows). Despite having a pathologic volume (0.68 mL) similar to that of the tumor focus in A, the tumor focus shown in C and D has a lower mean ADC (964.2 *10 6 mm$^2$/s). Note: Images A and C show only one representative slice out of 12 and 8 total histopathology slices, respectively. The tumors in (A) and (C) were both present on 7 contiguous slices.



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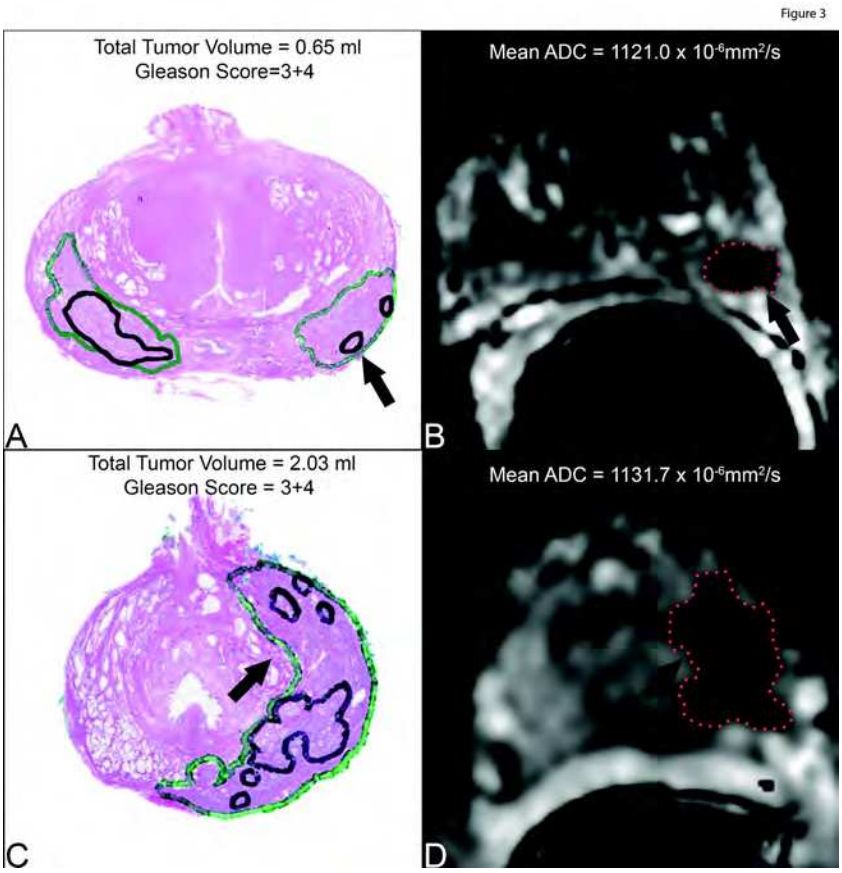
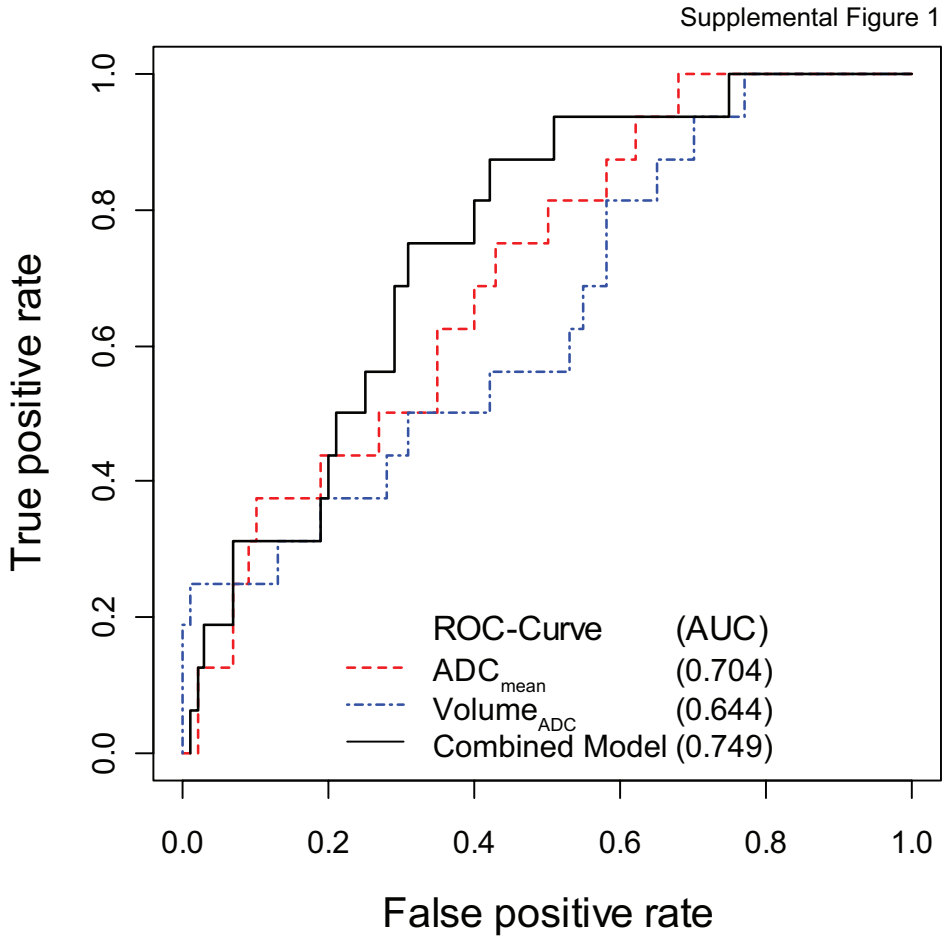
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

**Figure 3** – Top row: Whole-mount histopathology slice (A) and ADC map (b=0, 1000 s/mm$^2$) (B) demonstrating a PCa focus with a Gleason score of 3+4 (arrows), a mean ADC of 1121.0 *10-6 mm$^2$/s, and a total tumor volume of 0.65 mL. The bottom row shows a whole-mount histopathology slice (C) and ADC map (b=0, 1000 s/mm$^2$) (D) of another PCa focus with a Gleason score of 3+4 (arrows) and a histopathologic volume of 2.03 mL. The mean ADC value of the tumor focus in C and D (1131.7 *10 6 mm$^2$/s) is similar to that of the tumor focus in A and B, even though the volumes of the two foci differ substantially. Note: Images A and B show only one representative slice out of 8 and 9 total histopathology slices, respectively. The tumors in (A) and (B) were present on 5 and 7 contiguous slices, respectively.



## Supplemental Material

**Figure Caption Supplemental Figure 1** - Results of receiver operating characteristic (ROC) analysis for the identification of tumors with a Gleason score ≥ 7. A model combining mean tumor ADC value ($ADC_{mean}$) and tumor volume derived from ADC maps ($Volume_{ADC}$) performed only slightly better than $ADC_{mean}$ alone. (Note: AUC = area under ROC curve.)



## Supplemental Table 1 - Patient Demographics

| | Patients (n=131) |
|---|---|
| **Age at MRI (years); median (range)** | 60 (42-81) |
| **PSA at diagnosis [ng/mL]; median (range)** | 4.6 (0.5-33.9) |
| **Time between MRI and prostatectomy (days); median (range)** | 22 (1-168) |
| **Clinical Stage at Prostatectomy*; n (%)** | |
| T2a | 20 (15) |
| T2b | 68 (52) |
| T3a | 33 (25) |
| T3b | 8 (6) |
| T4 | 2 (2) |
| **GS at prostatectomy; n (%)** | |
| **3+3** | 26 (20) |
| **3+4** | 75 (57) |
| **4+3** | 22 (17) |
| **4+4** | 2 (1) |
| **4+5** | 5 (4) |
| **5+4** | 1 (1) |

*Staging according to AJCC 1997 (29). Note: GS = Gleason score.

## Supplemental Table 2 - Lesion Characteristics

| Total Lesions; n | **399** |
|---|---|
| Volume on histopathology [**mL**]; median (range) | 0.14 (0.003-14.35) |
| Total lesions > 0.5 **mL**; n (%) | 116 (29.1) |
| PZ; n (%) | 89 (76.7) |
| TZ; n (%) | 27 (23.3) |
| Volume [mL]; median (range) | 0.96 (0.51-14.35) |
| GS of lesions > 0.5 mL; n (%) | |
| 3+3 | 16 (13.8) |
| 3+4 | 73 (62.9) |
| 4+3 | 19 (16.4) |
| 4+4 | 2 (1.7) |
| 4+5 | 5 (4.3) |
| 5+5 | 1 (0.9) |

Note: PZ = peripheral zone; TZ = transition zone; GS = Gleason score

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# Prostate MRI: Evaluating tumor volume and apparent diffusion coefficient as surrogate biomarkers for predicting tumor Gleason score

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